

C4
concd

40
52. (new) The method of claim 1 wherein the supraphysiologic amount is up to 10 - 50 fold higher than the total normal plasma level concentration of the at least one vitamin $\div (V_p/V_D)^2$.

Remarks

Claims 1 - 43 and 48 - 50 are pending in the application. Claims 1, 3, 4 and 36 have been amended. New claims 51 and 52 have been added.

Support for amended claim 1 is found in the specification on pg. 11, lns. 14 - 17; pg. 20, lns. 7 - 9; Table 1 on pg. 21, and original claim 2. Support for amended claim 3 is found in Tables 1 - 2 on pgs. 21 - 22 of the specification. Support for amended claim 36 is found in the specification on pg. 11, lns. 14 - 17; pg. 20, lns. 7 - 9; and in Tables 1 - 2 on pgs. 21 - 22. Support for new claims 51 and 52 is found in Tables 1 - 2 on pgs. 21 - 22. A "marked up" version of the amended claims has been included herein as Appendix A, as required by 37 C.F.R. 1.121(c)(1)(ii).

Reconsideration is requested in view of the above changes and following remarks.

Response to the Section 102(b) rejection

Claims 36, 39, 41 and 42 are rejected under 35 U.S.C. 102(b) as allegedly anticipated by US Pat. No. 5,851,985 of Tepic et al. (Tepic). Applicants respectfully traverse the rejection.

Tepic published on December 22, 1998, which is less than a year before the filing date of the present application. Thus, Tepic is not a reference under section 102(b). Applicant presumes Examiner meant to apply this rejection under section 102(e).

Regardless, Tepic does not anticipate the present claims. Under 35 U.S.C. 102, every limitation of a claim must be identically shown in a single prior art reference for the reference to anticipate the claim. In re Bond, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990). "[A]bsence from the reference of any claim element negates anticipation." Kloster Speedsteel AB v. Crucible, Inc., 230 USPQ 81, 84 (Fed. Cir. 1986).

The claims as amended specify that the dialysate solution comprises at least folic acid, vitamin B₆, thiamine, or vitamin B₁₂ in less than the physiological amount or in a supraphysiologic amount. The specification on pg. 11, lns. 14 - 17 defines "physiological amount" as the amount needed to achieve a solution concentration within the range normally

found in serum, and a "supraphysiologic amount" as the amount needed to achieve a solution concentration higher than the range normally found in serum.

The Tepic dialysate solution is "supplemented by . . . organic or inorganic substances at concentrations *essentially equal* to those found in the normal blood plasma . . ." (Tepic col. 3, lns. 54 - 58, emphasis added). These supplemental substances include pyridoxal (vitamin B₆), thiamine and folic acid (Tepic, col. 15, lns. 10 - 11). Claim 36, as amended, require the present dialysate solution to contain folic acid, vitamin B₆, and/or thiamine in a concentration that is either less or more than that normally found in the blood plasma. Thus, claim 36 and dependent claims 39, 41 and 42 contain elements which are not disclosed in Tepic.

Because Tepic does not disclose every element of claims 36, 39, 41 and 42, this reference cannot support an anticipation rejection. Applicant respectfully requests that the 35 U.S.C. 102 rejection of these claims be withdrawn.

Response to the section 103(a) rejection

Claims 1 - 12, 19, 20, 22 - 28 and 33 - 34 are rejected under 35 U.S.C. 103(a) as allegedly rendered obvious by Tepic in view of US Pat. No. 5,108,767 of Mulchandani et al. (Mulchandani). Applicant respectfully disagrees.

To establish a *prima facie* case of obviousness, a reference or combination of references must: (1) suggest to those of ordinary skill in the art that they should make the claimed invention, and (2) reveal to those of ordinary skill in the art that they would have a reasonable expectation of success. In re Vaeck, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art and not in Applicant's disclosure. In re Dow Chemical Company, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Here, neither Tepic nor Mulchandani suggest to those of ordinary skill in the art that they should make the claimed invention, nor reveal a reasonable expectation of success in doing so.

The rejected claims are directed to a method for preventing or correcting a vitamin deficiency with a dialysate solution comprising less than a physiological amount or a supraphysiologic amount of folic acid, vitamin B₆, thiamine, and/or vitamin B₁₂.

Tepic is concerned with a dialysate solution for the treatment of cancer by hemodialysis, in which certain essential amino acids are eliminated from the solution or are

present in very low amounts. Examiner admits that Tepic does not disclose the use of supplemented dialysis solutions to correct vitamin deficiencies in dialysis patients (see ¶5 on pg. 3 of the Detailed Action). There is also no teaching or suggestion in Tepic that a dialysate solution can contain folic acid, vitamin B₆, thiamine, or vitamin B₁₂ in concentrations that are less than or greater than the physiological amount, as required by the present claims.

In fact, Tepic discloses that the concentrations of nutrients in the dialysate solution, other than one or two essential amino acids, must be “essentially equal” to the concentration of that nutrient in the blood plasma. Indeed, it appears that for renal dialysis patients not undergoing cancer treatment, there is no omission of essential amino acids from the dialysate solution (see Tepic col. 10, lns. 19 - 26).

Mulchandani discloses a nutrient solution to be taken *orally* by dialysis patients. See, for example, Mulchandani at col. 6, lns. 64 - 68 (which discusses addition of flavorings to the solution); col. 7, lns. 14 - 18 (which states the solution can be used as an oral supplement or as the primary source of nutrition); and col. 15, lns. 18 - 20 (which states that the solution is administered either by drinking or by tube feeding). Thus, the teachings of Mulchandani are not relevant to determining the concentrations of water-soluble vitamins in a dialysate solution, and provides no motivation to alter the teachings of Tepic to arrive at the presently claimed methods.

The present specification at pg. 20, lns. 7 - 9 discloses that certain vitamins bind to plasma proteins, and stresses that this binding must be taken into account when practicing the claimed methods. Table 1 on pg. 21 of the specification provides a guide for adjusting nutrient concentration in a dialysate solution based on the plasma protein binding characteristics of the vitamins, and the intended use of the solution.

Table 2 on pg. 22 of the specification discloses that folic acid, vitamin B₆, thiamine, and vitamin B₁₂ all bind to plasma proteins to a significant but undetermined extent (see esp. note 2). Table 1 indicates that a dialysate solution should contain such vitamins in less than physiological amounts (if used in every dialysis round to prevent vitamin deficiency), or in supraphysiologic amounts (if used intermittently to treat or prevent vitamin deficiency).

Neither Tepic or Mulchandani teach or disclose the importance of determining levels of folic acid, vitamin B₆, thiamine, and/or vitamin B₁₂ in a dialysate solution based on their plasma protein binding characteristics and the intended use of the solution. Moreover,

neither reference suggests that vitamin deficiencies can be treated or prevented with dialysate solutions containing less than physiologic amounts, or supraphysiologic amounts, of folic acid, vitamin B₆, thiamine, and vitamin B₁₂.

Thus, those of ordinary skill in the art could not arrive at the present invention from the teachings of Tepic and Mulchandani either alone or in combination; nor would these references provide a reasonable expectation that the claimed methods could be successfully practiced. Applicant submits that Examiner has not established a *prima facie* case of obviousness based upon Tepic and Mulchandani. The 35 U.S.C. 103(a) rejection of claims 1 - 12, 19, 20, 22 - 28 and 33 - 34 over these references should be withdrawn.

Claims 16 - 18, 31 - 32 and 38 are rejected under 35 U.S.C. 103(a) as allegedly rendered obvious by Tepic and Mulchandani in view of US Pat. No. 4,237,167 of Cavazza et al. (Cavazza). Applicant respectfully disagrees.

The rejected claims are directed to a dialysate solution comprising carnitine and less than physiologic amounts or supraphysiologic amounts of folic acid, vitamin B₆, thiamine, and/or vitamin B₁₂, and to methods of preventing or correcting vitamin deficiencies in dialysis patients with such a solution.

As discussed above, neither Tepic nor Mulchandani disclose or suggest dialysate solutions containing less than physiologic amounts, or supraphysiologic amounts, of folic acid, vitamin B₆, thiamine, and/or vitamin B₁₂, or that vitamin deficiencies can be treated or prevented with such solutions. Cavazza discloses the use of acyl carnitine in dialysis solutions to supplement depleted carnitine in dialysis patients. There is no disclosure or suggestion in Cavazza of including folic acid, vitamin B₆, thiamine, and/or vitamin B₁₂ in the dialysis solution. Thus, Cavazza provides no motivation to alter the teachings of Tepic or Mulchandani to arrive at the presently claimed solutions and methods. The 35 U.S.C. 103(a) rejection of claims 16 - 18, 31 - 32 and 38 is therefore improper, and should be withdrawn.

Claims 13 - 15, 29 - 30 and 37 are rejected under 35 U.S.C. 103(a) as allegedly rendered obvious by Tepic and Mulchandani in view of Pru et al. (1985), *Nephron* 39: 112-116 (Pru). Applicant respectfully disagrees.

The rejected claims are directed to dialysate solutions comprising vitamin C and less than physiologic amounts or supraphysiologic amounts of folic acid, vitamin B₆, thiamine, and/or vitamin B₁₂, and to methods of correcting or preventing vitamin deficiency with such solutions.

As discussed above, neither Tepic nor Mulchandani disclose or suggest dialysate solutions containing less than physiologic amounts, or supraphysiologic amounts, of the recited vitamins, or that vitamin deficiencies can be treated or prevented with such solutions. Pru discloses the addition of vitamin C to dialysate solutions to treat vitamin C deficiencies, but does not disclose the use of water soluble vitamins such as folic acid, vitamin B₆, thiamine, and/or vitamin B₁₂ in dialysate solutions. Thus, Pru provides no motivation to alter the teachings of Tepic or Mulchandani to arrive at the presently claimed solutions and methods. The 35 U.S.C. 103(a) rejection of claims 13 - 15, 29 - 30 and 37 is therefore improper, and should be withdrawn.

Claims 21, 35, 43 and 48 - 50 are rejected under 35 U.S.C. 103(a) as allegedly rendered obvious by Tepic in view of Mulchandani, Cavazza and Pru. Applicants respectfully disagree.

The rejected claims are directed to dialysate solutions comprising vitamin C, carnitine, certain mineral supplements and less than physiological or supraphysiologic amounts of folic acid, vitamin B₆, thiamine, vitamin B₁₂, and to methods of correcting or preventing vitamin deficiency with such solutions. As discussed above, none of the cited references, either alone or in combination, teaches or suggests the present claims. Tepic teaches a dialysate solution containing levels of folic acid, vitamin B₆, and thiamine that are essentially equal to the physiological amount. Mulchandani discloses a nutrient preparation for oral administration only. Neither Pru nor Cavazza teach that water-soluble vitamins can or should be added to dialysis solutions.

Thus, there is no motivation to combine the teachings of Tepic, Mulchandani, Cavazza or Pru to arrive at the presently claimed solutions and methods. The 35 U.S.C. 103(a) rejection of claims 21, 35, 43 and 48 - 50 is therefore improper, and should be withdrawn.

Conclusion

Based on the foregoing, all claims are believed in condition for allowance. An early and favorable action toward that end is earnestly solicited.

Respectfully submitted,

AJAY GUPTA

BY  _____

DANIEL A. MONACO
Registration No. 30,480
DRINKER, BIDDLE & REATH, LLP.
One Logan Square
18th and Cherry Streets
Philadelphia, PA 19103
(215) 988-3312 ph.
(215) 988-2757 fax
Attorney for Applicant

Appendix A – “Marked-up” Version of Amended Claims as Required Under 37 C.F.R. 1.121(c)(1)(ii)

1. (once amended) A method for preventing or correcting a vitamin deficiency in a dialysis patient comprising dialysis of the patient with a dialysate solution which comprises an effective amount of at least one vitamin selected from the group consisting of folic acid, vitamin B₆, thiamine, vitamin B₁₂, and pharmaceutically acceptable salts thereof, wherein the at least one vitamin is present in the dialysate solution in an amount less than a physiological amount or in a supraphysiologic amount.

3. (once amended) The method of claim [2] 1 wherein the vitamin deficiency is prevented by adding [at least] less than a physiological amount of the at least one vitamin to the dialysate solution.

4. (once amended) The method of claim [2] 1 wherein the vitamin deficiency is prevented or corrected by adding a supraphysiologic amount of the at least one vitamin to the dialysate solution.

36. (once amended) A dialysate solution comprising an effective amount of at least one vitamin selected from the group consisting of folic acid, vitamin B₆, thiamine, vitamin B₁₂, and pharmaceutically acceptable salts thereof, wherein the at least one vitamin is present in the dialysate solution in an amount less than a physiological amount or in a supraphysiologic amount.